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EXAMINER	
GABEL, GAILENE	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/081,118	Applicant(s) LEFEVRE ET AL.	
	Examiner Gailene R. Gabel	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-6,9-11 and 19-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-6,9-11 and 19-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and arguments, filed on April 24, 2006, is acknowledged and has been entered. Claims 12-18 have been cancelled. Claim 5 has been amended. Claims 22-25 have been added. Accordingly, claims 3-6, 9-11, and 19-25 are pending. Claims 3-6, 9-11, and 19-25 are under examination.

Withdrawn Rejections

2. All rejections not reiterated herein, have been withdrawn.

3. In light of Applicant's amendment and arguments, the rejection of claim 5 under 35 U.S.C. 112, second paragraph, is hereby, withdrawn.

New Matter

4. Claims 22-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In this case, the specification does not appear to provide literal or specific descriptive support for the recitation of "a mixture of saponins and at least one other non-ionic detergent" and "in a concentration of 0.1% to 10% (w/v)". Page 7, lines 5-28

of the specification appears to disclose a number of detergents used in the reagent including saponin, and specifically provides "a mixture of Triton X100 in a concentration of 0.05% (w/v) and Tween 20 in a concentration of 0.0001% (v/v)" as a specific embodiment of a detergent used with the reagent; however, it fails to provide literal support for "a mixture of saponins and at least one other non-ionic detergent" and "in a concentration of 0.1% to 10% (w/v)". Page 13, lines 5-8 also specifically provides a reagent composition [used] having detergents wherein "a mixture of Triton X100 in a concentration of 0.05% (w/v) and Tween 20 in a concentration of 0.0001% (v/v)" is specifically disclosed, but fails to provide literal support for the specific recitations in claims 22 and 23. Furthermore, none of the originally filed claims recited the limitations in question. Recitation of claim limitations lacking literal or specific descriptive support in the specification or originally filed claims constitutes new matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 3-6, 9-11, and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakata (US 5,496,734) in view of Haas et al. (Cation-Anion Cotransport, Methods in Enzymology, 173: 280-91 (1989)), and if necessary, in light of Applicant's French Patent no. 97 01090 (31 January 1997).

Sakata discloses a reagent for identifying, counting, and classifying blood cells. The reagent comprises a lysing agent which is quaternary ammonium salts at a concentration that lyses erythrocytes and a fluorescent stain that can permeate through permeabilized cell membrane of nucleated unlysed cells (leucocytes) so as to incorporate with and label intracellular nucleic acids of the unlysed nucleated cells (see column 6, line 64 to column 7, lines 1-67, column 8, lines 1-12, and especially column 10, lines 44-62). According to Sakata, nonionic surfactants may also be added to the reagent to control the effects of ionic surfactants toward cell membrane (see column 9, line 14 to column 10, line 4). Sakata provides that the surfactant may function by removing part of substances which constitute cell membrane; thus yielding pores in the cell membrane to allow passage of substances such as stain into the cell (see column 10, line 63 to column 11, line 8). Stains used with the reagent include Thiazole Orange, Acridine Orange, ethidium bromide, and propidium bromide (see column 8, lines 18-29). Sakata teaches that alcohol can be added as fixing agent to minimize loss of cytoplasms and granules and to optimize degree of damage of the cell membranes. According to Sakata, formaldehyde and gluteraldehyde are also used as fixing agents (see column 10, lines 10-39 and column 2, lines 13-19). The reagent further includes anticoagulant and buffer (see column 8, line 64 to column 9, line 13).

Sakata et al. differ from the instant invention in failing to teach incorporation of ionophore into a reagent for identifying and counting nucleated blood cells.

Haas et al. provide use of valinomycin in cation-anion cotransport, as an ionophore to demonstrate different cell membrane permeability of cells to specific

elements, i.e. sodium and potassium. Haas et al. specifically provide use of valinomycin as ionophore in conjunction with reagents or methods that employ potential sensitive dyes. Haas et al. show investigations of valinomycin with different cells and successfully demonstrated that there is electroneutrality of (Na+ + K+ + 2Cl-) cotransport in MDCK cells.

Applicant admits, by way of disclosure at page 4, lines 23-30, that inclusion of ionophores in a reagent solution assists in penetration of specific molecules into cells (selectively increases permeability of potential-sensitive molecules into cell membrane of blood cells as provided by Haas) and mentions such concept in Applicant's French Patent no. 97 01090, dated 31 January 1997. Accordingly, ionophores are known to inherently increase permeability of cell membranes to specific selected molecules.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate valinomycin as an ionophore as taught by Haas into the reagent taught by Sakata for use in identifying, counting, and classifying blood cells, because Haas specifically provided that ionophores such as antibiotics (valinomycin) are capable of increasing permeability of cell membrane in blood cells to charge-sensitive molecules, such characteristic being a known inherent property of ionohores in reagents, and such enhancement in hematological compositions having potential sensitive dyes including that taught and used by Sakata, allows for more accurate detection, identification, and classification of nucleated blood cells in a sample because it enhances penetration of specific stains and other molecules of the reagent into intracellular blood cell environment.

6. Claims 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakata (US 5,496,734) in view of Haas et al. (Cation-Anion Cotransport, Methods in Enzymology, 173: 280-91 (1989)), and if necessary, in light of Applicant's French Patent no. 97 01090 (31 January 1997) as applied to claims 3-6, 9-11, and 19-21, and further in view of Ledis et al. (US Patent 4,751,179).

Sakata, Haas et al., and also Applicant's French Patent no. 97 01090 are discussed supra. Sakata, Haas et al., and also Applicant's French Patent no. 97 01090 differ from the instant invention in failing to teach incorporating saponins and other non-ionic detergents into a reagent.

Ledis et al. disclose a reagent system having mixtures of saponins and other ionic or non-ionic detergents into hematological reagent to lyse red blood cells. Ledis et al. also disclose incorporation of glutaraldehyde into the reagent system. According to Ledis et al., the reagent system is used to causatively treat whole blood in order to stromatolyze anucleated red blood cells and modify nucleated leucocytes or white blood cells so as to differentially define and identify distinct clusters or populations via parameters including light scatter and fluorescence intensity. See Abstract.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate saponins with other detergents as taught by Ledis into the reagent and method taught by Sakata and modified by Haas because saponins in mixtures with other lysing agents are obvious variations of lysing detergent mixtures

known and commonly used in the hematological art for treating whole blood samples and removing interfering effects by red blood cells.

In as far as the concentration range of membrane fixing reagent used in the reagent, it is maintained that the amount of elements or components for incorporation into a reagent, are all result effective variables which the prior art references have shown may be altered in order to achieve optimum results. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454, 456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. at 458, 105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Since Applicant has not disclosed that the specific limitation recited in instant claim 23 is for any particular purpose or solve any stated problem, and various matrices, solutions and parameters appear to work equally as well, absent unexpected results, it would have been obvious for one of ordinary skill to discover the optimum workable ranges of the reagents and methods disclosed by the prior art by normal optimization procedures.

Response to Arguments

7. Applicant's arguments with respect to claims 3-6, 9-11, and 19-21 have been considered but are moot in view of the new grounds of rejection.

A) Applicant argues that the combination of Sakata with Haas et al. does not render obvious the claimed invention because Haas et al. neither describes nor suggests that valinomycin is an agent that promotes penetration of stain into cells to be marked. Applicant specifically contends that Haas et al. does not suggest that an ionophore could increase permeability of a cell to nucleic acid stain.

Contrary to Applicant's argument, Haas et al. specifically provide that valinomycin is an ionophore that is known, used, and compatible with reagents and methods that employ potential-sensitive stains or dyes, and provides its advantageous use in circumventing permeability of red cell membranes to specific charge sensitive molecules. Additionally, Applicant admits, by way of disclosure at page 4, lines 23-30, that inclusion of ionophores in a reagent solution assists in penetration of specific molecules into cells (selectively increases permeability of potential-sensitive molecules into cell membrane of blood cells as provided by Haas); such concept being taught and suggested early on in Applicant's French Patent no. 97 01090, dated 31 January 1997.

8. For reasons aforementioned, no claims are allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
Patent Examiner
Art Unit 1641
June 27, 2006

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